Water

Intro

We've filtered the blood. We've reabsorbed ions and glucose.

Two-thirds of the filtered sodium gets reabsorbed by the PCT. Two-thirds of the water gets reabsorbed by the PCT. Only 5% of filtered water and sodium get to the collecting duct. The last lesson was about the diluting segments, how they reabsorb what they reabsorb and the pharmacology that can manipulate those segments. But what we didn't talk about was what those segments were doing to the rest of the nephron, or to the interstitium around the tubules. In fact, we essentially equated apical reabsorption (from the lumen into the cell) with reabsorption back into the blood. But we didn't say what happens, or how. Now we're going to talk about that.

This lesson is about concentration gradients and the movement of water or solute to balance those concentration gradients. Now is when we talk about why the loop of Henle is a loop, and why the vasa recta must also be a loop. We are going to discuss countercurrent exchange, the cortex-to-medulla concentration gradient, how the loop of Henle takes care of most of the remaining reabsorption of ions and water, and then how what little bit gets to the collecting duct can be manipulated by hormones.

The Concentration Changes in the Interstitium

Through the magic of countercurrent exchange (explained below), there is a concentration gradient in the interstitium of the kidney. **Cortex** is about **300 mOsm**. The deeper into the medulla you go, the more concentrated the interstitium gets. **Inner medulla** is about **1,200 mOsm**. You have no idea how or why that is possible. Accept for a moment that it is.

The Vasa Recta

The vasa recta is in the shape of a loop. The vasa recta provides the peritubular capillaries that feed oxygen to the tubule cells of the loop of Henle.

The vasa recta's endothelium allows solutes and water to pass freely. The vasa recta quickly equilibrates to the interstitium. Because it is a loop, the lumen of the vasa recta concentrates the deeper in the medulla it goes, then dilutes as it returns to cortex. That means the **interstitium and the vasa recta are effectively the same thing** for this discussion.

If the vasa recta were not a loop, it would simply take the high concentration away to the veins, and the concentration gradient would be lost.

The Tubules

The segments of the tubules do not allow solutes and water to pass freely. Therefore, the tubules do not quickly equilibrate with the interstitium. The PCT always delivers the descending loop of Henle an isotonic (300 mOsm) tubular fluid. Along the nephron the permeability to water and ions changes.

For this discussion, we are not talking about apical transporters bringing solutes into the cytoplasm. We are talking about the net outcome of each segment.

Besides the PCT, the **descending loop of Henle** is **permeable to water**. Water can move into and out of the descending loop of Henle. Because it receives 300 mOsm tubular fluid and because the interstitium gets more concentrated, water is only going to leave the descending loop of Henle (more on this in a bit). The descending loop of Henle is the concentrating segment.

The **ascending loop of Henle** isn't just permeable to sodium, it **actively pumps sodium into the interstitium**. Actively, as in it uses ATP to push sodium against its concentration gradient out of the tubules into the interstitium. This is going to be key to countercurrent magic.

The distal convoluted tubule continues to remove solute, but it isn't really involved in countercurrent exchange or establishing the concentration gradient.

The collecting duct is the subject of an entire section in this lesson. The collecting duct can be induced to be permeable to sodium (aldosterone) or permeable to water (antidiuretic hormone).

Explaining Countercurrent Magic When it's Already Established

Water flows from an area of lower concentration to higher concentration. There is no such thing as a water pump. The only way water moves, either into or out of the tubule, is if the segment is permeable to water. The only segment that is permeable to water is the descending limb of Henle. In the nephron, **water leaves the descending limb of Henle** into the interstitium.

Sodium chloride from here on will be referred to as salt. Forget what you know about sodium gradients driving reabsorption, getting sodium into the cytoplasm of the tubule cell. You know that even though sodium is passively reabsorbed into the cytoplasm, it must be actively pumped out the basolateral membrane into the interstitium. For this discussion on countercurrent exchange, **salt leaves the tubule in the ascending limb** by primary active transport.

The concentration gradient has already been established. The interstitium of the cortex is 300 mOsm, the concentration of the interstitium increases as you go deeper into the medulla, and the deepest medulla is 1,200 mOsm. The proximal convoluted tubule ALWAYS gives the descending loop of Henle **isotonic** tubule fluid (which is 300 mOsm).

The **descending loop of Henle** is **freely permeable to water** but **impermeable to salt**. As that urine of 300 mOsm descends the medulla, the interstitium gets more and more concentrated. To balance the concentration gradient between the lumen and the interstitium, two things could happen. Water could leave the tubule or salt could enter the tubule. But because the descending limb is permeable only to water, only one of those two things happens—water moves out of the tubule and into the interstitium. This equilibrates the concentration of the urine to the concentration of the interstitium. The fluid in the tubule becomes concentrated.

The loop of Henle takes a hairpin turn. The permeability completely changes. The tubules are **impermeable to water** and **actively pump sodium**. As the loop of Henle takes its turn, water permeability changes. The tubule not in the deepest medulla gains some water as it begins to rise. But right around 1,100 mOsm in the tubule, the ascending limb starts pumping sodium. The "countercurrent multiplier" is about 200 mOsm. The very first segment of thick ascending limb pumps out 100 mOsm worth of sodium. The tubule changes to 1,000 mOsm, the interstitium 1,200 mOsm.

That 1,000 mOsm urine continues up the ascending limb. Where the countercurrent multiplier is applied again. One hundred mOsm of sodium pumped out. The tubule is 900 mOsm, the interstitium 1,000 mOsm. That 900 mOsm urine moves on, countercurrent multiplier, 800 mOsm in the tubule, 600 mOsm in the interstitium. Now, of course the process isn't as discrete as "100 mOsm every set distance." It is a gradual process. But this breaking it down by 100 mOsm is easier for the human brain to understand.

At the very top of the tubule, in the distal convoluted tubule, the cortex is isotonic (300 mOsm) and the tubule fluid is 100 mOsm; again, a difference of 200 mOsm.

What we just explained is that once the gradient is established, the gradient continues to be established. This explains only the gradient, not how the gradient came to be.

What we also just explained is how almost all of the remaining filtered water and sodium gets reabsorbed. Because of the concentration gradient established by countercurrent exchange, almost all of the water is reabsorbed from the tubules into the interstitium in the descending limb. Then, most of the sodium is reabsorbed in the ascending limb. And because the vasa recta and the interstitium rapidly equilibrate, that means the water and sodium reabsorbed in the loop of Henle does end up in the bloodstream.

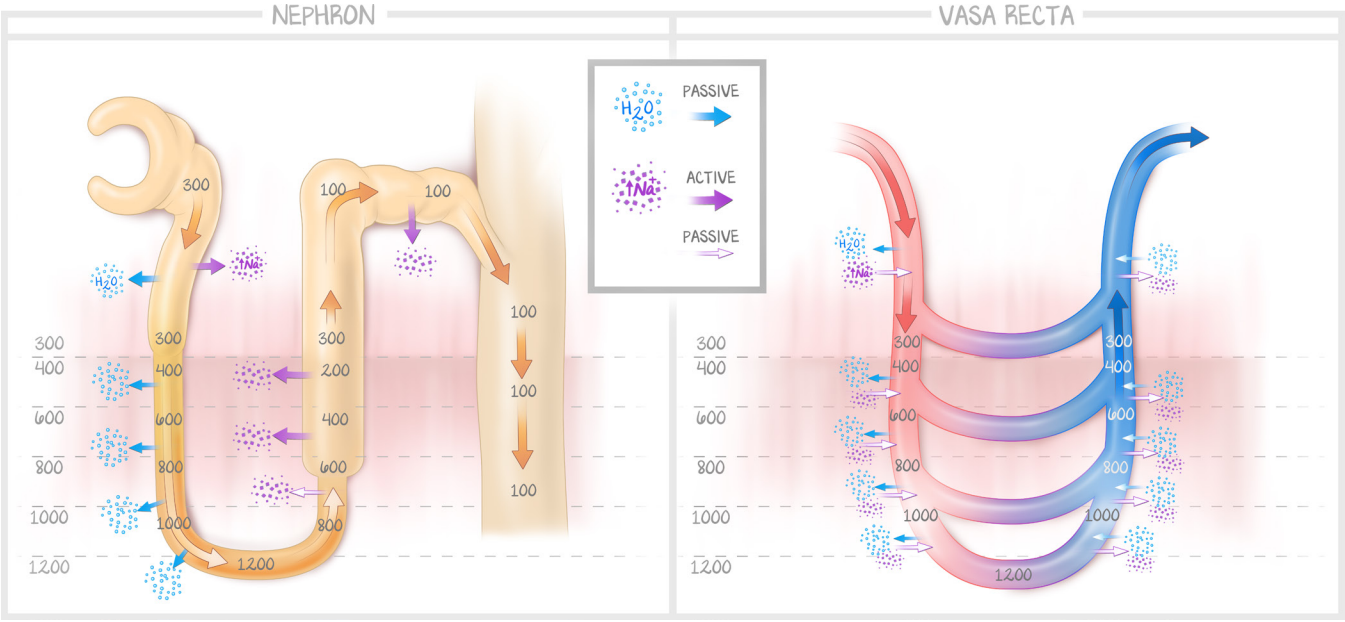

Figure 5.1: Continuation of Countercurrent Exchange
As the descending loop of Henle encounters more and more concentrated interstitium, more and more water is reabsorbed into that interstitium because the descending loop of Henle is permeable to water. As the ascending loop of Henle is impermeable to water and actively pumps sodium into the interstitium, the lumen dilutes and the interstitium is kept concentrated. At the end of the ascending loop, the lumen concentration is 100, and interstitium 200. The vasa recta is freely permeable to water and sodium. It descends and equilibrates, then ascends and equilibrates. The vasa recta is designed to not compromise the interstitium's concentration gradient.

Concentration Gradient and the Collecting Duct

Countercurrent exchange develops a concentration gradient from cortex to medulla. That concentration gradient is designed to absorb most of the remaining water and solutes not reabsorbed by the PCT but that still makes it to the collecting duct. The collecting duct receives only 5% of the filtered water and sodium. Sodium can either be wasted (no aldosterone) or reabsorbed (aldosterone). In the last lesson, we briefly mentioned the effects of aquaporin channels. This section expands on that subject.

After the DCT, the concentration of the urine is 100 mOsm. There is water and salt in there. As the collecting duct descends the medulla towards the calyces, the concentration of the interstitium increases, from 300 mOsm to 1,200 mOsm. That means at every point along the collecting duct there is a driving force to move water from the tubules to the interstitium. That driving force only gets stronger the deeper into the collecting duct the fluid goes. But the collecting duct remains impermeable to water unless told to become permeable by **antidiuretic hormone**.

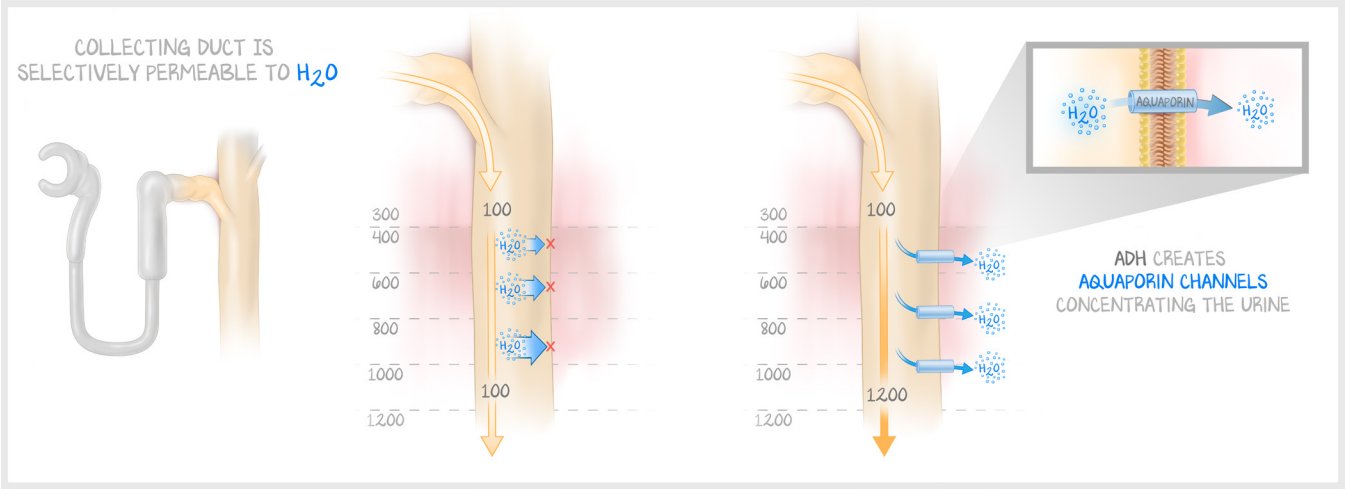

Figure 5.2: Concentration and the Collecting Duct
The descending limb reabsorbs water. The ascending limb reabsorbs salt and establishes the countercurrent exchange. The DCT reabsorbs sodium. The concentration of the filtrate at the start of the concentration duct is 100 mOsm. The driving force for water reabsorption is high, and only gets higher as the collecting duct descends. Water will be reabsorbed if the collecting duct becomes permeable to water. That concentration force is realized by the insertion of aquaporin channels under the influence of antidiuretic hormone.

The mechanisms regulating ADH release from the posterior pituitary are not relevant for this discussion (Endocrine #3: *The Unhealthy Posterior Pituitary*). Here's what you need to know for the kidney.

If ADH is present, it binds to ADH receptors on the basolateral membrane of principal cells of the collecting duct. ADH-receptor activation results in the insertion of **aquaporin channels** into the apical membrane. Aqua- (water) -porin (pore) makes the collecting duct membrane permeable to water. Because water has always had a driving force to leave the lumen, in the presence of ADH, water exits the lumen into the plasma. The water is reabsorbed into the body, thereby **concentrating the urine**.

When ADH is on, water leaves the lumen, and the urine concentrates. When ADH is off, water stays in the lumen, and the urine dilutes. Therefore countercurrent exchange establishes a concentration gradient both to ensure that most of the filtered water and substrates are reabsorbed by the nephron, but also to allow the collecting duct to regulate water balance by diluting urine (giving away free water) or concentrating urine (taking free water back) from the tubule fluid.

Okay, now the moment you've all been waiting for (or dreading). We've seen the concentration gradient established by countercurrent exchange. Now what the hell is countercurrent exchange, and how did the gradient get established in the first place?

Establishing the Gradient with Countercurrent Exchange

Countercurrent implies a flow of one thing in the opposite direction of the flow of another thing. Sort of like how the descending limb goes down towards the medulla and the ascending loop of Henle goes up towards the cortex. Countercurrent. Exchange sounds like you need to trade something. One current, the descending limb, trades its water for the other current, the ascending limb's sodium. "Countercurrent exchange" just means "establishing the gradient."

We are going to start with a theoretical nephron. There is no concentration gradient. The cortex is 300 mOsm. The inner medulla is 300 mOsm. The urine tubule is 300 mOsm. Everything is 300 mOsm.

All at once, magically, every segment that can pump sodium, does. Everywhere, all at once in the ascending tubule, 100 mOsm of sodium is ejected into the interstitium. The osmolarity of the lumen becomes 200 mOsm. The osmolarity of the interstitium becomes 400 mOsm. The descending limb is permeable to water. All at once, for the entire length of the tubule, water leaves the descending tubule, and the entire descending tubule is 400 mOsm.

A 300 mOsm urine from the PCT pushes all the urine down one. The 400 mOsm urine that was deepest in the medulla takes the turn. Countercurrent magic. At this level of the nephron, the ascending limb becomes 300 mOsm and the interstitium 500mOsm. At the same time, water leaves the descending limb to equilibrate to 500mOsm.

For a moment, let's attend only to the hairpin turn. Five hundred mOsm tubule fluid cycles around the hairpin. Countercurrent exchange magic. Four hundred mOsm tubule fluid, 600 mOsm interstitial. The descending limb meets the interstitial fluid. Now, the 600 mOsm tubule fluid cycles around the hairpin. Countercurrent magic. Tubules 500 mOsm, interstitium 700 mOsm. And so on it goes.

Now, let's attend to what happened to that concentrated urine that got passed up the tubule. The 400 mOsm tubule fluid got passed up the ascending limb. Countercurrent magic. Three hundred mOsm tubule and 500 mOsm interstitium. The descending limb matches. That 300 mOsm tubule fluid gets passed up the tubule. Countercurrent magic. Two hundred mOsm tubule, 400 mOsm interstitium. That 200 mOsm gets passed up, countercurrent, 300 mOsm.

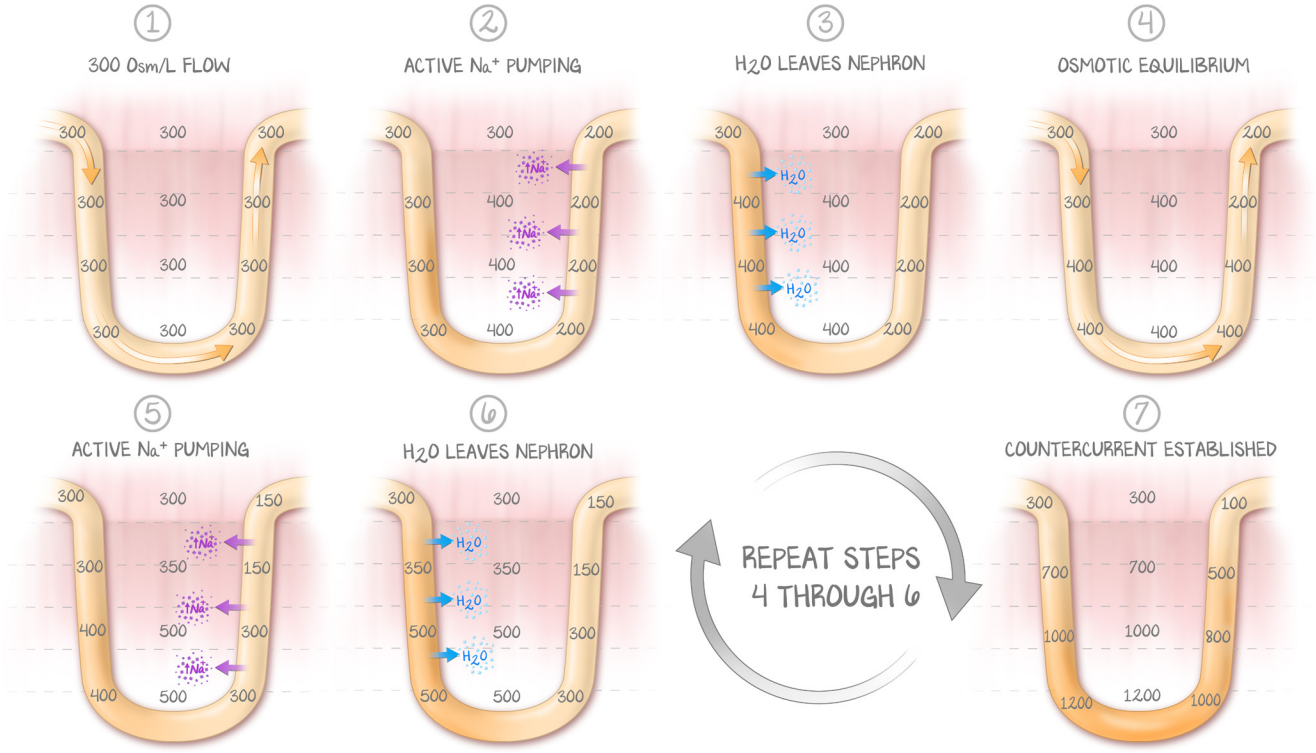

Figure 5.3: Establishing Countercurrent Exchange
Visual representation of the discussion in the text.

And now let's attend to everything. As more-concentrated urine comes around the hairpin, the deepest medulla interstitium gets even more concentrated by the active pumping by the ascending limb. The more concentrated the urine becomes around the turn, the more concentrated it will be as it is passed up the ascending limb, getting progressively more dilute as it is repeatedly countercurrent exchanged. The limit of this system to the interstitium is at 1,200 mOsm at the medulla's deepest, most concentrated, and 300 mOsm of the cortex, most dilute. Because the countercurrent multiplier (which is just the difference between the tubule concentration and the interstitium concentration) is 200 mOsm, the most dilute the DCT gets, which is in the cortex, is 100 mOsm.

Urea

We just explained how you can get an osmolarity gradient using NaCl only. But the astute reader realizes that the descending limb gets to 1,200 mOsm . . . why doesn't the ascending limb start pumping at 1,200 mOsm? Because **urea**.

Urea enters the collecting duct, where the urine is dilute. Urea can do whatever it wants—it doesn't need a channel. So, it will move from a region with higher concentration of urea to a region with lower concentration.

If ADH is on and water gets reabsorbed, the concentration of the urine increases. Since urea is dissolved in the water of the urine, if the concentration of the urine increases, the concentration of urea increases. The more water that gets reabsorbed, the higher the concentration of urea in the tubule. And since urea does not require a transport protein, it will travel down its concentration gradient into the interstitium.

If ADH is off and water is not absorbed, the concentration of the filtrate remains dilute. Just the reverse of the last paragraph. A more dilute urine means a lower concentration of urea. If the filtrate remains dilute, urea stays in the tubule and is lost in the urine.

Urea accounts for **40% of the osmolarity** of the interstitium. NaCl is actively pumped out in TAL, that is actively generating the gradient, and therefore is termed **active countercurrent exchange**. Because urea is not pumped actively, it is said to be **passive countercurrent exchange**.

What?

We recommend not learning urea or its role in kidney function. Urea is the way nitrogenous waste is eliminated from our body. Made by the liver, excreted by the kidney. The fractional excretion of sodium, as we've said, is a useless test. When someone is on a diuretic, which can contaminate the fractional excretion of sodium, it has been suggested that the use of a fractional excretion of urea be used instead. A surrogate test for a test you should never perform. Does not sound like a good idea to us.